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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,723	04/25/2007	Jeffrey C. Miller	8325-0036.31 (S36-US3)	2253
20855 ROBINS & PA	7590 05/11/201 STERNAK	0	EXAMINER	
1731 EMBARC	CADERO ROAD	DUNSTON, JENNIFER ANN		
	SUITE 230 PALO ALTO, CA 94303		ART UNIT	PAPER NUMBER
			1636	
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			05/11/2010	PAPER

# Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(s)				
Office Action Comments	10/587,723	MILLER ET AL.				
Office Action Summary	Examiner	Art Unit				
	Jennifer Dunston	1636				
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply						
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.  - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).						
Status						
1) Responsive to communication(s) filed on						
	-· action is non-final.					
·—	, <del></del>					
•	closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213.					
olosed in describing with the probled direct Ex parte Quayle, 1000 C.B. 11, 400 C.B. 210.						
Disposition of Claims						
4)⊠ Claim(s) <u>1-14</u> is/are pending in the application.	☑ Claim(s) <u>1-14</u> is/are pending in the application.					
4a) Of the above claim(s) is/are withdray	4a) Of the above claim(s) is/are withdrawn from consideration.					
5) Claim(s) is/are allowed.						
6)⊠ Claim(s) <u>1-14</u> is/are rejected.						
7) Claim(s) is/are objected to.						
Application Papers						
9)⊠ The specification is objected to by the Examiner.						
10)⊠ The drawing(s) filed on <u>27 July 2006</u> is/are: a)⊠ accepted or b)□ objected to by the Examiner.						
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).						
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).						
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.						
Priority under 35 U.S.C. § 119						
<ul> <li>12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</li> <li>a) All b) Some * c) None of:</li> <li>1. Certified copies of the priority documents have been received.</li> <li>2. Certified copies of the priority documents have been received in Application No</li> <li>3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).</li> <li>* See the attached detailed Office action for a list of the certified copies not received.</li> </ul>						
Attachment(s)  1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 4/25/2007; 4/22/2008.	4)  Interview Summary Paper No(s)/Mail Da 5)  Notice of Informal P 6)  Other:	te				

#### **DETAILED ACTION**

Receipt is acknowledged of an amendment, filed 4/25/2007, in which claim 1 was amended. Claims 1-14 are pending and under consideration.

#### **Priority**

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the

required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required.

Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

In the instant case, reference to Application No. 10/912,932 in the first sentence of the specification. However, the relationship between the instant application and Application No. 10/912,932 has not been provided. The reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

# Information Disclosure Statement

Receipt of information disclosure statements, filed on 4/25/2007 and 4/22/2008, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

### **Specification**

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 27, line 25.

The use of the trademark GENBANK (page 27, lines 22 and 23), SUPERSCRIPT (page 113, line 28), HIGH PURE (page 98, line 11), LIPOFECTAMINE (page 99, line 23; page 103, line 29), and OPTI-MEM (page 99, line 23) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

## **Double Patenting**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-10 of copending Application No. 11/304,981 ('981 application) in view of Chandrasegaran (US Patent No. 5,916,794, cited as reference A10 on the IDS filed 4/25/2007; see the entire reference).

Claims 1 and 3-10 of the '981 application are drawn to a method for deleting sequences in a region of interest in double-stranded DNA of genomic cellular chromatin in a cell, the method comprising: expressing first, second, third and fourth fusion proteins in the cell, each of the fusion protein comprising: (i) a zinc finger DNA-biding domain that binds to a target site in the DNA, and (ii) a cleavage half-domain; further wherein (a) the first and second fusion proteins bind to first and second target sites respectively, wherein a first cleavage site lies between the first and second target sites, and (b) the third and fourth fusion protein bind to third and fourth target sites respectively, wherein a second cleavage site lies between the third and fourth target sites; such that the first and second fusion proteins cleave the DNA at the first cleavage site, the third and fourth fusion proteins cleave the DNA at the second cleavage site, and the DNA ends are rejoined such that sequences between the first and second cleavage sites are deleted. Claim 3 requires the first and second cleavage sites to be on the same chromosome. Claim 4 requires the first and second target sites to be separated by between 4 and 6 nucleotide pairs. Claim 6 requires the first and second target sites to be separated by between 4 and 6 nucleotide pairs.

The claims of the '981 application are broader in some aspects as compared to the present claims in that they do not require the step of engineering the zinc finger binding domains to bind to at least the first and second target nucleotide sequences and do not require at least one of the fusion proteins to comprise the cleavage domain at the N-terminus. However, Chandrasegaran teaches a method for cleaving cellular chromatin in a gene of interest in a human, animal or plant cell, the method comprising the steps of (i) selecting the region of interest and engineering or designing zinc finger DNA-binding proteins to bind to target sites; (ii) linking the designed or engineered zinc finger DNA-binding domains to a nuclease domain, such as a FokI nuclease domain to create a protein that is capable of cleaving and enzymatically inactivating the target DNA; and (iii) introducing the nuclease into the cells by preparing a gene delivery vehicle containing a gene encoding the nuclease and delivering the gene delivery vehicle to the cells, wherein the nuclease binds and cleaves DNA in the gene of interest (e.g., Abstract; column 1, lines 22-28; column 2, lines 33-37; column 2, line 48 to column 3, line 27; column 3, lines 46-65; column 11, lines 35-53; column 13, lines 35-48; column 15, lines 1-18). Chandrasegaran teaches the method where the nuclease generally comprises a DNA-binding domain and nuclease domain and exemplifies fusion proteins, such as ZF-QQR-F<sub>N</sub>, where the zinc finger DNAbinding domain is N-terminal to the cleavage domain (e.g., column 3, lines 46-65; column 6 line 52 to column 7, line 12). However, Chandrasegaran explicitly teach that a DNA-binding protein, MutS, can be linked to the FokI cleavage domain so that the FokI nuclease domain is at the Nterminal end of the hybrid protein or at the C-terminal end of they hybrid protein (e.g., column 18, lines 20-31). Thus, it would have been obvious to one of ordinary skill in the art to select the target sites, and engineer the zinc finger binding domains to specifically bind the target sites in

order to achieve the expected benefit of providing the binding domains to specifically target the intended regions, such as the CCR-5 gene of claim 7 of the '981 application. Because Chandrasegaran generally teaches the fusion of zinc finger binding domains and FokI cleavage half-domains without limiting the order of the domains and later teaches that a MutS DNA binding protein can be fused either N-terminal or C-terminal relative to the FokI cleavage half domain to result in a functional protein, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of cleaving cellular chromatin of Chandrasegaran where the fusion proteins comprise the zinc finger binding domain either N-terminal or C-terminal to the FokI nuclease domain in order to achieve the predictable result of providing active zinc finger nucleases for the cleavage of cellular chromatin.

This is a provisional obviousness-type double patenting rejection.

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6, 7, 12, 13, 18, 21, 22, 27-43, 45-51 and 55-61 of copending Application No. 10/912,932 (hereinafter the '932 application) in view of Chandrasegaran (US Patent No. 5,916,794, cited as reference A10 on the IDS filed 4/25/2007; see the entire reference).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to method for cleaving genomic cellular chromatin in a region of interest by selecting the region of interest, designing zinc finger binding domains to bind to first and second nucleotide sequences in the region of interest, and expressing fusion proteins comprising the zinc finger binding domain and FokI cleavage half-domains. The

present claims are narrower in scope than the claims of the '932 application in that they require at lest one of the first or second zinc finger fusion proteins to comprise the cleavage half-domain closer to the N-terminus and the zinc finger binding domain closer to the N-terminus. However, Chandrasegaran generally teaches the fusion of zinc finger binding domains and FokI cleavage half-domains without limiting the order of the domains and later teaches that a MutS DNA binding protein can be fused either N-terminal or C-terminal relative to the FokI cleavage half domain to result in a functional protein (e.g., column 3, lines 53-65; column 18, lines 20-31). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of cleaving cellular chromatin of Chandrasegaran where the fusion proteins comprise the zinc finger binding domain either N-terminal or C-terminal to the FokI nuclease domain in order to achieve the predictable result of providing active zinc finger nucleases for the cleavage of cellular chromatin.

This is a provisional obviousness-type double patenting rejection.

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-27 of copending Application No. 12/456,857 (hereinafter the '857 application) in view of Chandrasegaran (US Patent No. 5,916,794, cited as reference A10 on the IDS filed 4/25/2007; see the entire reference).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to method for cleaving genomic cellular chromatin in a region of interest by selecting the region of interest, designing zinc finger binding domains to bind to first and second nucleotide sequences in the region of interest, and expressing

fusion proteins comprising the zinc finger binding domain and FokI cleavage half-domains. The present claims are narrower in scope than the claims of the '932 application in that they require at lest one of the first or second zinc finger fusion proteins to comprise the cleavage half-domain closer to the N-terminus and the zinc finger binding domain closer to the N-terminus. However, Chandrasegaran generally teaches the fusion of zinc finger binding domains and FokI cleavage half-domains without limiting the order of the domains and later teaches that a MutS DNA binding protein can be fused either N-terminal or C-terminal relative to the FokI cleavage half domain to result in a functional protein (e.g., column 3, lines 53-65; column 18, lines 20-31). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of cleaving cellular chromatin of Chandrasegaran where the fusion proteins comprise the zinc finger binding domain either N-terminal or C-terminal to the FokI nuclease domain in order to achieve the predictable result of providing active zinc finger nucleases for the cleavage of cellular chromatin.

This is a provisional obviousness-type double patenting rejection.

#### Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chandrasegaran (US Patent No. 5,916,794, cited as reference A10 on the IDS filed 4/25/2007; see the entire reference) in view of Smith et al (Nucleic Acids Research, Vol. 28, No. 17, pages 3361-3369, 2000, cited as reference C85 on the IDS filed 4/25/2007; see the entire reference).

Chandrasegaran teaches a method for cleaving cellular chromatin in a gene of interest in a human, animal or plant cell, the method comprising the steps of (i) selecting the region of interest and engineering or designing zinc finger DNA-binding proteins to bind to target sites; (ii) linking the designed or engineered zinc finger DNA-binding domains to a nuclease domain, such as a FokI nuclease domain to create a protein that is capable of cleaving and enzymatically inactivating the target DNA; and (iii) introducing the nuclease into the cells by preparing a gene delivery vehicle containing a gene encoding the nuclease and delivering the gene delivery vehicle to the cells, wherein the nuclease binds and cleaves DNA in the gene of interest (e.g., Abstract; column 1, lines 22-28; column 2, lines 33-37; column 2, line 48 to column 3, line 27; column 3, lines 46-65; column 11, lines 35-53; column 13, lines 35-48; column 15, lines 1-18). Chandrasegaran teaches the method where the nuclease generally comprises a DNA-binding domain and nuclease domain and exemplifies fusion proteins, such as ZF-QQR-F<sub>N</sub>, where the zinc finger DNA-binding domain is N-terminal to the cleavage domain (e.g., column 3, lines 46-

65; column 6 line 52 to column 7, line 12). However, Chandrasegaran explicitly teach that a DNA-binding protein, MutS, can be linked to the FokI cleavage domain so that the FokI nuclease domain is at the N-terminal end of the hybrid protein or at the C-terminal end of they hybrid protein (e.g., column 18, lines 20-31).

Chandrasegaran does not teach the method where the zinc finger DNA-binding domains are engineered to bind to first and second target sequences located between 2 and 50 nucleotides from the first sequence, where the first and second target sequences are on the same strand or opposite strand of DNA.

Smith et al teach that chimeric nucleases with several different specificities based on zinc finger recognition have already been constructed and characterized (e.g., page 3361, right column 2<sup>nd</sup> full paragraph). Smith et al teach the further characterization of DNA cleavage by two of these zinc finger-FokI cleavage half-domain (F<sub>N</sub>) chimeras: Zif-QQR-F<sub>N</sub> (QQR) and Zif-ΔQNK-F<sub>N</sub> (QNK) (e.g., paragraph bridging pages 3361-3362). Smith et al teach that the enzymes require two copies of the recognition site in close proximity to effect efficient double-strand cleavage, reflecting a requirement for dimerization of the cleavage domain (e.g., page 3362, left column, 1<sup>st</sup> full paragraph; page 3365, right column, full paragraph). Smith et al teach that both tail-to-tail inverted repeats (binding sites on the opposite strand) and direct repeats (binding sites on the same strand separated by 10 bp) are effectively cut by the QQR nuclease (e.g., page 3362, paragraph bridging columns; page 3363, paragraph bridging columns; Figure 2). Further, Smith et al teach that the separation of the binding sites has an effect on cleavage efficiency with separations of 8, 14 and 28 bp supporting cleavage between the two binding sites with zinc finger nuclease fusion protein comprising a (G<sub>4</sub>S)<sub>3</sub> linker (e.g., paragraph bridging

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pages 3363-3364; page 3364, left column, 1st full paragraph; Figure 1). Smith et al teach that the finding that paired binding sites are required for efficient dimerization and cleavage shows precisely what type of target will be susceptible to cleavage by the zinc finger nucleases (e.g., paragraph bridging pages 3368-3369). Smith et al provide models of binding of the fusion proteins to DNA and explain that the linker provides the extension necessary even for the cleavage of direct repeats (e.g., pages 3367-3368, Molecular modeling; Figure 8). In order to cleave at an arbitrarily determined location, two 9 bp DNA sequences in inverted orientation and separated by 6-35 bp should be selected, and zinc finger combinations that bind these sequences specifically would then be derived by design or selection and linked to the FokI cleavage domain (e.g., paragraph bridging pages 3368-3369). Smith et al teach that the feasibility of the approach to make *in vivo* chromosomal breaks has been demonstrated in a separate study where the binding sites of the zinc finger nucleases were incorporated into chromatin (e.g., page 3369, left column, 2<sup>nd</sup> full paragraph).

The claims require the first and second fusion proteins to comprise the following orientations: (i) at least one zinc finger fusion protein where the cleavage half-domain is closer to the N-terminus and the zinc finger binding domain is closer to the C-terminus (claims 1-10 and 12); (ii) both fusion proteins comprising the cleavage half-domains closer to the N-termini and the zinc finger binding domains closer to the C-termini (claim 11); and (iii) one fusion protein comprising the cleavage half-domain closer to the N-terminus, and the zinc finger binding domain closer to the C-terminus, and the other comprising the zinc finger binding domain closer to the N-terminus, and the cleavage half-domain closer to the C-terminus (claims 13 and 14).

Because Chandrasegaran generally teaches the fusion of zinc finger binding domains and FokI

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cleavage half-domains without limiting the order of the domains and later teaches that a MutS DNA binding protein can be fused either N-terminal or C-terminal relative to the FokI cleavage half domain to result in a functional protein, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of cleaving cellular chromatin of Chandrasegaran where the fusion proteins comprise the zinc finger binding domain either N-terminal or C-terminal to the nuclease domain in order to achieve the predictable result of providing active zinc finger nucleases for the cleavage of cellular chromatin.

The claims also require a spacing of 2 and 50 nucleotides between two binding sites recognized by a first and second zinc finger fusion protein. Because Chandrasegaran teaches zinc finger fusion proteins where the zinc finger binding domain and FokI nuclease domain are linked by a linker of  $(G_4S)_3$ , and Smith et al teach that a spacing of 10bp is functional for direct repeats (two binding sites on the same DNA strand) and a spacing of 6-35 should be selected for inverted repeats (two binding sites on opposite DNA strands) for a zinc finger nuclease fusion protein that also comprises a linker of  $(G_4S)_3$ , it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the orientation and spacing of the binding sites taught by Smith et al in order to achieve the predictable result of providing the proper orientation and spacing to obtain cleavage of the DNA at the target site.

### Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/ Examiner Art Unit 1636